# Functional matrix metalloproteinase-9 polymorphism (C-1562T) associated with abdominal aortic aneurysm

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***Purpose:*** **Matrix metalloproteinase-9 (MMP-9) is a potent endopeptidase with activity against both collagens and elastin. Expression of MMP-9 is elevated in vascular disease, and in particular within aneurysm tissues. This study tested the hypothesis that the functionally more active T allele of the MMP9 C-1562T polymorphism may be overrepresented in patients with abdominal aortic aneurysm (AAA) compared with control subjects and patients with atherosclerotic peripheral vascular disease (PVD).**
***Methods:*** **Seven hundred eighty-nine unrelated persons (AAA, n = 414; control subjects, n = 203; PVD, n = 172) were genotyped for the common C-1562T functional promoter polymorphism of the MMP9 gene.**
***Results:*** **Genotypes containing the T allele of this polymorphism were significantly more common in patients with AAA compared with both control subjects and patients with PVD (adjusted odds ratio, 2.41 and 2.94, respectively). The greatest shift between groups was observed in male patients, with a difference of 20.6% in CT/TT genotypes. and 12.1% in T allele frequency between patients with AAA compared with patients with PVD.**
***Conclusions:*** **This study provides further evidence to support the role of MMP-9 in the pathogenesis of AAA, and indicates that the MMP9 C-1562T functional polymorphism may represent a genetic component contributing to susceptibility to this vascular disease. (J Vasc Surg 2003;38:1363-7.)**

***Clinical Relevance:*** **Enzymes that degrade connective tissue components, particularly collagens and elastin, have been implicated in the pathogenesis of aneurysmal vascular disease. A strong genetic component is associated with susceptibility to abdominal aortic aneurysm (AAA). This study identifies a genetic marker associated with increased production of matrix metalloproteinase-9, a potent connective tissue protease, which may increase susceptibility to AAA formation. Clinical screening for such genetic markers might allow future detection of persons at high risk for AAA.**

Previously we reported a familial incidence of approximately 19% within a predominantly white population with abdominal aortic aneurysm (AAA),[1] an observation consistent with a strong genetic component, as described by other investigators.[2,3] The increased frequency of the 5G allele of an insertion/deletion polymorphism in the promoter region of the plasminogen activator inhibitor-1 (PAI-1) gene in patients with familial AAA compared with patients with sporadic AAA and control subjects[4] also supports this contention. The PAI-1 5G allele is associated with reduced PAI-1 transcription and a relative increase in tissue plasminogen activator activity, and thus may, in turn, lead to increased activation of matrix metalloproteinase (MMP) species.[5]

The MMPs have been widely implicated in the pathogenesis of both atherosclerosis [6,7] and AAA.[8-10] In particular, MMP-9 appears to be upregulated in both atherosclerotic disease[7,11] and aortic aneurysm disease.[12-14] However, patterns of cellular expression[12] and significantly higher MMP-9 expression in AAA [8,15] may contribute to phenotypic differences. Moreover, recent work in transgenic mice has raised the possibility that MMPs may have atheroprotective but proaneurysm activity.[16]

A relatively common cytosine to thymidine transition at position −1562 within the promoter region of the MMP9 gene results in an approximately 1.5-fold increase in promoter activity.[6] On the basis of known overexpression of this gene in AAA,[8,15] the relative frequency of this functional polymorphism was investigated in patients with AAA and patients with (atherosclerotic) peripheral vascular disease (PVD) and compared with a control population.

## METHODS

**Subjects.** In this study 789 unrelated subjects from the Otago/Southland region of New Zealand were examined. This population consisted of three groups comprising patients with AAA (n = 414), patients with PVD (n = 172), and a control group (n = 203). All AAAs were greater than 5 cm in diameter, necessitating surgical repair. A subset of patients with AAA (74/414, 17.9%) were identified as having a familial history (one or more first-degree family members with an AAA). PVD was defined as significant stenosis in multiple segments, including clinical symptoms such as claudication, rest pain, or tissue loss. Diagnosis was further confirmed with ankle-brachial index less than 0.7, pulse volume recordings, and arteriography.

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Competition of interest: none.
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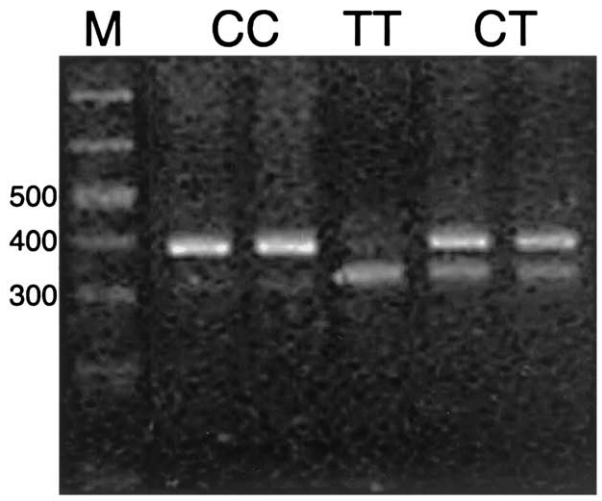
0741-5214/2003/$30.00 + 0
doi:10.1016/S0741-5214(03)01027-9




Ethidium bromide–stained agarose gel of MMP9 C-1562T genotype products. The 379 base pair (bp) polymerase chain reaction product was digested with BbuI. Sequences with a C allele at the −1562 polymorphic site were not digested by this restriction enzyme (undigested 379 bp fragment), whereas those with a T allele were cleaved into two fragments (320 bp fragment visible on gel). Lanes: *M,* DNA marker ladder; *CC,* C allele homozygotes; *TT,* T allele homozygote; *CT,* heterozygotes.

Patients with PVD also underwent abdominal ultrasound examination, to exclude those with concurrent AAA. Patients with PVD were excluded if maximum anteroposterior aortic diameter was greater than 2.5 cm. Control subjects were recruited from local community groups, with inclusion criteria of age greater than 55 years and current good general health.

All subjects were given a questionnaire to ascertain demographic vascular risk factors. Information collected included age and gender, and history of hypertension, hyperlipidemia, diabetes (type collected but grouped for analysis), stroke, ischemic heart disease, and PVD. Smoking habits (current and past) were assessed, and the number of pack-years was calculated (1 pack-year equaled 20 cigarettes per day for 1 year). Plasma samples were also collected, and lipoprotein A (Lp(a)) levels were analyzed with sandwich enzyme-linked immunosorbent assay.

**Genotyping.** Genomic DNA was extracted from blood samples with a modified salting-out procedure, and were diluted to 50 ng/μL. The C to T transition at position −1562 in the MMP9 gene was examined with a modification of the method described by Zhang et al.[6] In brief, a polymerase chain reaction (PCR) amplification was conducted with forward (5′-CAACGTAGTGAAACCCCATCTCT) and reverse (5′-TCCAGGCCCAATTATCACACTTAT) primers. The resulting 379 base-pair (bp) PCR product was subjected to restriction enzyme digestion with Bbu1 (Promega Biosciences, San Luis Obispo, Calif) and was run on a 3% Seakem LE agarose gel (BMA Products, Rockland, Me). Alleles were represented by 379 bp (C) or 320 bp (T) product bands (Fig).

Undigested PCR product was sequenced (ABI Prism 377 DNA sequencer) to confirm homology with the MMP9 promoter (GenBank accession number D10051). Reference samples of both homozygote genotypes were run with each restriction enzyme digest.

**Statistical analysis.** Statistical analysis was performed with StatView version 5.01 (SAS Institute, Cary, NC). Genotype and allele frequencies were compared with $\chi g^2$ tests. For continuous variables, analysis of variance with the Fisher protected least significant difference test was performed. Multiple logistic regression was used to test interactive effects of variables.

## RESULTS

Several significant differences were noted in demographic factors between groups, including gender ratio, smoking history (pack-years), plasma Lp(a) level, and history of hypertension, hypercholesterolemia, and diabetes (Table I). Number of pack-years, plasma Lp(a) level, and history of hypertension and hypercholesterolemia were all greater in patients with AAA or PVD compared with control subjects. Although the incidence of diabetes in the PVD group was significantly greater than in the other groups, there was no significant difference between patients with AAA and control subjects. The rate of diabetes in patients with familial AAA was 1.33%, compared with 7.1% in those with no known family history (sporadic) of AAA ($P = .058$) and 6.7% in controls ($P = .089$). Unadjusted odds ratios for these risk factors, with control subjects as the reference population, are shown in Table II. A subanalysis of the control population, excluding those with a history of ischemic heart disease, resulted in reductions in all demographic risk factors (Table I), and consequently had the effect of increasing the odds ratios for demographic risk factors in both the AAA and PVD groups.

Gender was a significant confounding variable in several risk factor parameters, including age ($P = .001$), hypertension ($P = .003$), smoking pack-years ($P < .0001$), and plasma Lp(a) level ($P = .036$). All but pack-years were greater in female patients.

The genotype distributions for the MMP9 C-1562T polymorphism were in Hardy-Weinberg equilibrium. There was a significant difference in genotype frequency between groups, with more CT heterozygotes or TT homozygotes observed in patients with AAA compared with control subjects ($P = .025$) or patients with PVD ($P = .003$; Table III). There was no difference between control subjects and patients with PVD or between patients with familial or sporadic AAA.

A significant gender difference in the C-1562T polymorphism genotype frequency was observed in the total cohort ($P = .005$). Whereas this effect remained significant in patients with PVD ($P = .001$), it was only suggestive in patients with AAA ($P = .117$) and not significant in the control group. Consequently, the greatest frequency shift was observed after splitting populations by gender, with a 20.6% shift in CT/TT genotypes and a 12.1% shift in T allele frequency observed between male patients with AAA

**Table I.** Demographic data

| | *Control group (N = 203)* | *Control subjects with history of IHD excluded (N = 167)* | *AAA group (N = 414)* | *PVD group (N = 172)* |
|---|---|---|---|---|
| Age (± 1 SD) (y) | 70.8 ± 8.0 | 70.1 ± 8.1* | 71.7 ± 7.6 | 72.2 ± 8.8 |
| Gender (% male) | 48.0 | 46.5 | 72.2† | 57.1 |
| Hypertension (%) | 33.3‡ | 28.3‡ | 55.2§ | 64.9 |
| Hypercholesterolemia (%) | 18.1‖ | 11.1‡ | 30.0¶ | 40.7 |
| Diabetes (%) | 6.7 | 5.6 | 6.1 | 24.1# |
| IHD (%) | 17.7** | 0 | 42.6§ | 32.0 |
| PVD (%) | 0.0‡ | 0 | 23.4† | 100 |
| Smoking (pack-years ± 1 SD) | 11.6 ± 19.1‡ | 9.8 ± 16.6‡ | 31.2 ± 29.7 | 37.1 ± 37.8 |
| Plasma Lp(a) (nmol/L ± 1 SD) | 50.7 ± 66.7* | 46.6 ± 63.8* | 76.5 ± 104.3 | 72.0 ± 97.1 |

*IHD,* Ischemic heart disease; *AAA,* abdominal aortic aneurysm; *PVD,* peripheral vascular disease; *Lp(a),* lipoprotein A.
Removal of subjects with history of IHD from control population reduced rates of all demographic risk factors in this group, but did not significantly alter relationships observed between control group and AAA and PVD groups.
Data represent mean ± 1 SD.
Significant differences vs: *AAA or PVD ($P < .05$); †control or PVD ($P < .0001$); ‡AAA or PVD ($P < .0001$); §PVD ($P < .03$); ‖AAA ($P < .004$) or PVD ($P < .0001$); ¶PVD ($P < .002$); #AAA or control ($P < .0001$); **AAA ($P < .0001$) or PVD ($P = .004$).

**Table II.** Odds ratios for groups with vascular disease

| *Reference group* | *AAA* | | | | *PVD* | | | |
|---|---|---|---|---|---|---|---|---|
| | *All control subjects* | | *Control subjects with history of IHD excluded* | | *All control subjects* | | *Control subjects with history of IHD excluded* | |
| | *OR* | *CI* | *OR* | *CI* | *OR* | *CI* | *OR* | *CI* |
| Age (y) | 1.01 | 0.99-1.03 | 1.02 | 1.002-1.047* | 1.02 | 0.99-1.03 | 1.03 | 1.007-1.062* |
| Gender (male) | 3.67 | 2.56-5.24† | 3.90 | 2.67-5.70† | 1.44 | 0.96-2.17 | 1.54 | 1.004-2.35* |
| Hypertension | 2.47 | 1.72-3.52† | 3.12 | 2.10-4.64† | 3.71 | 2.40-5.71† | 4.69 | 2.95-7.47† |
| Hypercholesterolemia | 1.94 | 1.27-2.96‡ | 2.41 | 1.49-3.91‡ | 3.10 | 1.92-5.01† | 3.86 | 2.27-6.58† |
| Diabetes | 0.90 | 0.45-1.79 | 0.85 | 0.49-1.92 | 4.43 | 2.29-8.58† | 5.34 | 2.50-11.38† |
| Ischemic heart disease | 3.41 | 2.24-5.18† | | N/A | 2.20 | 1.33-3.52§ | | N/A |
| Smoking (per 10 pack-years) | 1.55 | 1.39-1.74† | 1.71 | 1.50-1.96† | 1.64 | 1.45-1.84† | 1.80 | 1.57-2.07† |
| Plasma Lp(a) (>75 nmol/L) | 1.64 | 0.99-2.70 | 1.82 | 1.05-3.16* | 1.52 | 0.88-2.62 | 1.65 | 0.91-2.97 |
| MMP9 C-1562T (T allele) | 1.53 | 1.05-2.23* | 1.61 | 1.07-2.40* | 0.84 | 0.52-1.34 | 0.88 | 0.54-1.43 |
| Adjusted MMP9 C-1562T | 2.41 | 1.44-4.02† | 2.43 | 1.38-4.27‡ | 0.84 | 0.41-1.74 | 0.86 | 0.41-1.84 |

*AAA,* Abdominal aortic aneurysm; *PVD,* peripheral vascular disease; *OR,* odds ratio; *CI,* 95% confidence interval; *Lp(a),* lipoprotein; *MMP,* matrix metalloproteinase.
In AAA group, strongest odds ratios were associated with male gender, history of ischemic heart disease, hypertension, T allele–containing MMP9 genotypes, and hypercholesterolemia. In contrast, whereas history of hypertension, hypercholesterolemia, and ischemic heart disease were also significant risk factors for PVD, MMP9 genotype and male gender were not significantly associated with this disease group. Diabetes, which had the greatest odds ratio of any risk factor in the PVD group, was not associated with AAA.
Odds ratios for the MMP9 T allele were adjusted for significant confounding effects by gender, smoking history (pack-years), and plasma Lp(a).
*$P < .05$; †$P < .0005$, ‡$P < .005$, §$P < .01$.

and PVD (Table IV), with the rarer T allele associated with patients with AAA.

Logistic regression analysis of MMP9 C-1562T genotype frequency indicated confounding effects by gender, smoking history (pack-years), and plasma Lp(a). With multiple logistic regression modeling to account for these variables, the T allele containing genotypes had an odds ratio of 2.41 (Table II) in patients with AAA compared with control subjects, and 2.94 (95% confidence interval, 1.57-5.45) compared with patients with PVD. This relationship was not significantly altered when modeled with the control subset without history of ischemic heart disease as the reference population (Table II).

## DISCUSSION

The MMPs represent a family of endopeptidases with activity against connective tissue matrix proteins. MMP-9 (gelatinase B or 92 kDa type IV collagenase) is a potent elastase and collagenase that has been implicated in the pathogenesis of atherosclerosis and aneurysm formation.[5,13,14,17-20] Of interest, however, levels of MMP-9 may be twice as high in aneurysmal arteries compared with those with occlusive lesions.[14,18] Rupture and expansion rates of AAAs have been linked to MMP-9 levels in tissue[21,22] and plasma.[23,24] Such observations appear consistent with the increased medial atrophy observed within AAAs, because activated MMPs may weaken the media by

**Table III.** Genotype and allele frequencies in AAA, control, and PVD groups (both sexes)

| | *AAA (N = 414)* | *Control (N = 203)* | *PVD (N = 172)* |
|---|---|---|---|
| Genotype (%) | | | |
| CC | 62.1 | 71.5 | 75.0 |
| CT | 35.0 | 28.0 | 25.0 |
| TT | 2.9 | 0.5 | 0.0 |
| Allele (%) | | | |
| C | 79.6 | 85.5 | 87.5 |
| T | 20.4 | 14.5 | 12.5 |

*AAA,* abdominal aortic aneurysm; *PVD,* peripheral vascular disease.
Genotype frequency: ($\chi^2$ test, $P = .0026$), AAA vs Control ($P = .030$) or PVD ($P = .003$), PVD vs Control ($P = .505$).
Allele frequency: ($\chi^2$ test, $P = .263$), AAA vs PVD ($P = .123$), AAA vs Control ($P = .259$), PVD vs Control ($P = .674$).

**Table IV.** Male genotype and allele frequencies in AAA, Control, and PVD groups

| | *AAA (N = 320)* | *Control (N = 97)* | *PVD (N = 98)* |
|---|---|---|---|
| Genotype (%) | | | |
| CC | 63.9 | 71.9 | 84.5 |
| CT | 32.7 | 27.0 | 15.5 |
| TT | 3.4 | 1.1 | 0.0 |
| Allele (%) | | | |
| C | 79.2 | 85.4 | 92.3 |
| T | 19.8 | 14.6 | 7.7 |

*AAA,* abdominal aortic aneurysm; *PVD,* peripheral vascular disease.
Genotype frequency: ($\chi^2$ test, $P = .0019$), AAA vs Control ($P = .262$) or PVD ($P = .0004$), PVD vs Control ($P = .084$).
Allele frequency: ($\chi^2$ test, $P = .048$), AAA vs PVD ($P = .013$), AAA vs Control ($P = .334$), PVD vs Control ($P = .121$).

causing destruction of elastic and collagen fibers and smooth muscle cells.[5]

In this study, the functional C-1562T MMP9 promoter polymorphism was examined in patients with AAA compared with both control subjects and patients with (atherosclerotic) PVD. No differences in either genotype or allele frequency were observed between control subjects and patients with PVD. The control population demonstrated an incidence of the T allele and T allele–containing genotypes in close accord with that reported previously in control groups.[6,25] Moreover, both the allele and genotype frequencies in patients with PVD closely matched those reported in patients with coronary artery disease,[26] with T allele–containing genotype frequency of 25.0% (PVD) versus 22.9% (coronary artery disease), and T allele frequency of 12.5% and 12.3%, respectively. On the basis of these observations, it was therefore not surprising that exclusion of control subjects with a history of ischemic heart disease from the reference population had no effect on the MMP9 T allele odds ratios associated with AAA.

There was a clear bias toward CT heterozygotes and TT homozygotes in patients with AAA compared with both the control subjects and patients with PVD in this study. The greatest shift in CT/TT genotype frequency was 20.6%, between male patients with AAA and PVD, with a corresponding shift in T allele frequency of 12.1%. The T allele of the C-1562T MMP9 polymorphism is associated with approximately 50% greater promoter activity than that of the C allele[6]; therefore, the observed shift in genotype and allele frequencies appears consistent with the elevated expression of MMP-9 in patients with AAA compared with patients with occlusive atherosclerotic disease.[8,27] Moreover, because expression of MMP-9 in AAA is associated with macrophages within a predominantly inflammatory environment, the observation of a genetic factor that leads to increased inducible expression of the MMP9 gene supports the potential importance of this polymorphism as a susceptibility factor in AAA.

In this study we observed C-1562T MMP9 gender effects, which were significant in the PVD group and suggestive in the AAA group, but not observed in the control group. Of interest, Wang et al[26] reported no gender effect in a relatively large group (n = 788) of patients with coronary artery stenosis. Nevertheless, patient gender represented a significant confounding factor at logistic regression analysis in this study.

Smoking history, as measured by the number of pack-years, was also a confounding variable on C-1562T MMP9 genotype in all three groups examined. This is an interesting observation, given a previously reported associated between the T allele of this polymorphism and smoking-induced emphysema.[28]

Previously, we reported decreased frequency of the 4G allele in the PAI-1 4G/5G polymorphism in patients with familial AAA compared with patients with sporadic AAA and control subjects.[4] We hypothesized that this may result in increased activation of MMPs in the subgroup with familial AAA. However, we did not observe any difference between patients with familial and sporadic AAA with regard to frequency of the MMP9 C-1562T polymorphism in the current study.

Associations between functional polymorphisms of various MMPs and aneurysms have also been investigated. Yoon et al[29] examined the association between AAA and the frequency of a length polymorphism in the CA repeat at nucleotide positions −131 to −90 of the MMP9 promoter as well as the MMP3 5A/6A polymorphism. A suggestive association between AAA and the MMP3 5A/6A polymorphism was described, but no difference in the MMP9 promoter CA repeat length polymorphism was observed. It should be noted, however, that the study by Yoon et al[29] comprised only 47 patients with AAA and was most likely underpowered. Moreover, the significant association observed in the current study involves a different MMP9 promoter polymorphism.

This report is the first to show that the C-1562T MMP9 promoter polymorphism is a strong independent risk factor for AAA. The T allele–containing genotypes of this polymorphism were associated with AAA with adjusted odds ratio of 2.41 compared with control subjects. Only male gender, history of hypertension, and previous isch-

emic heart disease carried greater risk odds. The greatest MMP9 T allele odds ratio, 2.94, was observed when the AAA group was compared with the clinically well-defined PVD group, in whom AAA had been excluded at ultrasound scanning. This observation both highlights the potential importance of this polymorphism as a susceptibility factor in AAA and supports the notion that AAA and atherosclerotic occlusive PVD may be distinct pathophysiologic entities.

In conclusion, the functionally more active T variant of the C-1562T MMP9 polymorphism was significantly associated with AAA compared with control or atherosclerotic PVD. This observation is consistent with the increased MMP-9 expression observed in aneurysmal aortic disease, and may represent an important genetic component contributing to AAA susceptibility.

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Submitted Mar 27, 2003; accepted Jun 17, 2003.